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Orofacial Dyskinesia

Clinical Features, Mechanisms and Drug Therapy

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Orofacial or tardive dyskinesias are involuntary repetitive movements of the mouth and face. In most cases, they occur in older psychotic patients who are in institutions and in whom long-term treatment with antipsychotic drugs of the phenothiazine and butyrophenone groups is being carried out. These dyskinesias are frequent in occurrence and characteristically are irreversible. Several biochemical mechanisms have been proposed as causes, including hypersensitivity or partially deneverated brain dopamine receptors and low affinity of the offending drugs for brain muscarinic cholinergic receptors. Clinical therapy has been attempted primarily with drugs that antagonize dopamine receptors or deplete brain dopamine. The benefits of drug treatment have been variable and lack of consistent improvement has been discouraging. Early recognition of dyskinesia should be attempted, and the dose reduced or the drug omitted at the first sign.

DRUG THERAPY of certain disorders, especially treatment of schizophrenia with phenothiazines and parkinsonism with L-dopa, has been associated with the emergence of certain abnormal involuntary movements termed dyskinesias.[1-4] These are involuntary, repetitive and stereotyped movements, involving the head, face and oral structures. In their typical presentation, tardive or orofacial dyskinesias consist of tongue protrusion with licking of the lips, sucking and smacking movements with the lips, chewing movements, grunting and similar sounds, puffing of the cheeks, forehead furrowing and eye opening and closing. In many cases, the limbs and trunk are also involved. When drug-induced, these manifestations may appear at any point during the drug treatment, including while the drug is being given, after termination of treatment or upon reinstitution of treatment. In many cases, the dyskinesias persist for months or years and there is poor response to drug manipulation or they are irreversible. The significance of orofacial dyskinesias is underscored by the fact that these now appear to be the major side effect limiting the use of the antipsychotic drugs, which are currently the most frequent cause of dyskinesia. Similar movements were reported to occur following epidemic en-

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cephalitis in the first part of the 20 century[5] and as being among the clinical features of certain basal ganglia disorders such as Huntington's chorea,[6] Sydenham's chorea[7] and Wilson's disease.[8]

This review will focus on clinical characteristics, basic mechanisms and therapeutic approaches. Drug-induced dyskinesias will be stressed because drugs are at present the most frequent cause of dyskinesias. The major responsible drugs are the phenothiazines and butyrophenones,[9] which are the two main classes of antipsychotic or neuroleptic agents (defined as drugs that cause psychomotor slowing and emotional quieting). Since the available literature on orofacial dyskinesias has grown enormously in recent years, the emphasis will be on concepts and therapeutic approaches rather than comprehensive citation of all the reports.

Clinical Features

A variety of terms have been applied to these involuntary dyskinetic movements, including tardive dyskinesia, orobuccolingual dyskinesia, facial dyskinesia, extrapyramidal insufficiency syndrome, drug-induced dyskinesia, cephalic dyskinesia and dyskinetic syndrome. Tardive dyskinesia, the first of these terms, was applied at first to abnormal orofacial movements that appear only following a long course of treatment or even after the discontinuation of therapy with the implicated drug, and hence the designation that the dyskinesia is "tardive."[2] However, because in some cases the dyskinesia occurs even in the early phases of the administration of the offending drug or the history of drug exposure is uncertain, it may be more appropriate to use the broader term of orofacial dyskinesia, since this denotes both the topography of involvement as well as the type of abnormal movement. Most cases of dyskinesia are drug-induced; however, in some cases there is no history of drug exposure. Of this latter group, in some patients there is a history of brain damage, electroconvulsive therapy (ECT) or previous surgical operation involving the brain, while relatively few of the cases are idiopathic. In many cases, the orofacial dyskinesia is accompanied by cervical or truncal dyskinesias (including involvement of respiratory function) and limb dyskinesias, including choreoathetosis, ballismus, myoclonus, dystonia, and restless legs (akathisia). However, the orofacial component is often the most disturbing to the patient and to the family for several reasons. Besides the obvious cosmetic disfigurement, orofacial involvement may significantly impair the important functions of eating, speaking and in some cases breathing.[10] These movements appear to be a common expression of a diverse group of disorders and occur in patients in whom dyskinesia is part of a more generalized disorder or in whom it is the major if not solitary manifestation. Thus it may be most appropriate to view orofacial dyskinesia as part of a symptom complex rather than as a specific expression of particular diseases.

The clinical history of this disorder, including incidence, predisposing factors, spontaneous remissions and responsiveness to drugs is not fully known and is disputed at best. The reported frequency of occurrence has ranged from as little as 0.5 percent of patients being treated with phenothiazines to as high as 41 percent.[11] There was an overall 17.6 percent incidence in a review of 22 reported series involving 22,399 patients treated with neuroleptics.[11] Several factors that may account for this discrepancy include variable definition of the syndrome and differentiation from other extrapyramidal syndromes, differing patient populations (especially regarding drug usage) and different techniques of assessing clinical status. A recent estimate suggests that drug-induced dyskinesias occur in 3 to 6 percent of psychiatric patients and in approximately 20 percent of elderly patients who are long-term or frequent residents of institutions.[12]

Orofacial dyskinesias should be clearly differentiated from other abnormal movements, especially those arising after exposure to neuroleptic drugs. Other extrapyramidal syndromes are acute dystonic reaction, drug-induced parkinsonism and akathisia.[2,12] Acute dystonic reactions typically occur in younger rather than in older patients and in males more than in females. Since they appear within a day or two of initial drug use, they reflect individual sensitivity to the drug used and respond promptly to parenteral administration of antihistamines or antiparkinsonian agents. Drug-induced parkinsonism is characterized primarily by rigidity, tremor and bradykinesia rather than by hyperkinesia, and is reversed by discontinuing administration of the drug or reducing the dose. Akathisia or the "restless legs" syndrome is characterized by an uncontrollable state of constant motion consisting of relentless pacing (tasikinesia) or repetitive movements especially of the legs, such as foot tapping or alternate adduction and abduction. This condition usually responds to a reduction of drug dosage or addition of a sedative. The relative incidence of the different extrapyramidal complications has been reported as parkinsonian in 38 to 48 percent, orofacial dyskinesia in 41 percent and akathisia in 22 percent of the patients receiving long-term therapy with trifluoperazine.[13] Of a series of 3,775 phenothiazine-treated patients, akathisia was noted in 21 percent, parkinsonism in 15 percent and dyskinesia in 2.3 percent.[14] However, this last category combined cases of acute dystonic reaction with those of orofacial dyskinesia. Despite this grouping, these results serve to suggest a low occurrence rate for these two side effects.

It has been suggested that underlying brain damage predisposes to orofacial dyskinesia.[15] Furthermore, most neuroleptic-induced dyskinesias occur in chronic schizophrenics receiving long-term pharmacotherapy, many of whom have been treated in the past with leukotomies or electroconvulsive therapy. Dementia has been associated with drug-induced dyskinesias and has been suggested to support the role of underlying brain damage. In one series, all 13 women with phenothiazine-induced dyskinesia were demented.[16] Of 29 cases related to phenothiazine and reserpine treatment, 12 (or 41.3 percent) were either demented or had a history of organic brain damage.[17] By contrast, the occurrence of dementia was not statistically increased in 213 patients with with dyskinesia.[18] In this last series, the overall incidence of dementia in 45.5 percent of the total of 683 patients studied appears high, especially since patients from the "subnormal ward" were excluded. No relationship between dementia and dyskinesia was observed in a nursing home population in which dementia occurred in 36 percent of those with dyskinesia and in 33 percent of those without dyskinesia.[19] No relationship was shown between dyskinesia and a variety of brain lesions, including head trauma, central nervous system infections, vascular disease, underlying medical diseases or treatment with ECT or insulin shock.[20] Therefore, it seems that brain damage is not a prerequisite to drug-induced dyskinesias.

The fact that most cases of dyskinesia have been reported in patients with chronic psychosis or dementia indicates that these are the patients who receive long-term therapy with neuroleptic drugs. There is no evidence indicating that chronic psychosis is a prerequisite or plays a specific role in the dyskinesias. This is supported by the reports of dyskinesia occurring in nonpsychotic patients treated with neuroleptics for personality disorders, psychoneurosis, gastrointestinal symptoms and chronic pain.[2,20-23]

Other forms of psychiatric treatment that alter brain function have been studied for possible causal association. A two-fold increase in the incidence of drug-induced dyskinesias was reported in 127 patients who had received electroconvulsive therapy compared with that in 86 patients who had not.[2] By contrast, no definite relationship between orofacial dyskinesia and electroconvulsive therapy could be shown to exist in 214 cases when compared with 468 other cases in which electroconvulsive therapy was not used.[18]

Prefrontal leukotomy in 105 patients was not reported to predispose to dyskinesias.[2,18] Insulin coma treatment in 55 patients was associated with an incidence of drug dyskinesia lower than that in patients who did not receive such treatment.[18]

Assessment of the role of brain damage in the production of dyskinesias may also be approached by neuropathologic examination. In the largest series, brains of 28 patients with dyskinesia were compared with those in 28 controls matched for diagnosis (15 with schizophrenia, 8 with senile dementia and 4 with other forms of psychoses).[24] Of the dyskinetic group, degeneration of substantia nigra cells was seen in 27, compared with only 7 in the control series. Gliosis of the midbrain and brainstem was found in 25 of the dyskinetic group but in only 4 of the control group. In a report of two cases, gliosis of the caudate nucleus together with nerve cell satellitosis and neuronophagia was noted.[25] In contrast to the pronounced differences reported in these two series, no specific lesions were found in the brains of three dyskinetic patients.[26] These neuropathological studies suggest that there is a higher incidence of neuropathologic change in the striatal nigral pathway, and this may predispose to neuroleptic-induced dyskinesias, but the evidence is not conclusive.

Brain damage appears to predispose to L-dopa-induced dyskinesias—L-dopa being the major drug besides neuroleptics associated with orofacial dyskinesia. Dopa-induced dyskinesias have been observed only in parkinsonian patients and never in control patients given L-dopa.[27,28] However, control patients have not been exposed to prolonged high dose treatment and may not be directly comparable to parkinsonian patients.

Age appears to be an important factor, with a higher incidence reported in older patients. In one series of 910 cases, the incidence of drug-induced dyskinesias in those under 50 years of age was 3.8 percent of males and 13 percent of females, while in those over 50 years of age, the incidence rose to 20 percent of men and 35 percent of women.[18] Similar results were reported for a series of 398 patients, in which less than 5 percent of those under 44 years but 33 percent of those older than 65 years were found to have dyskinesia.[11]

Women are affected more often than men by neuroleptic induced dyskinesias, with reported ratios of 2 to 1 up to 5 to 1.[13,16,18] Other reports suggest an equal incidence between the sexes.[11,29,30] It has been suggested that the apparently higher incidence in women actually reflects the increased number of older women receiving neuroleptics in institutions.[31] Of interest is the higher incidence of more severe cases among women as shown when mild or doubtful cases are eliminated.[13] These results are summarized in Table 1.

Administration of drugs for increasing periods appears to increase the risk of dyskinesias. In a series of 109 cases, the incidence was 2.7 percent after less than six months of treatment, 5.5 percent after six months to a year of treatment, 29 percent for one to three years of treatment and 31 percent for more than three years of treatment.[2] These results suggest that with continued therapy the risk of dyskinesias developing does not increase appreciably after the first year of therapy. Similar results have been reported more recently in a series of 85 neuroleptic-treated patients, all over 65 years of age, who were studied in three groups.[11] Of 28 patients treated for six months, in only two, or 7.1 percent did dyskinesias develop. Of those treated for more than five years, the incidence rose to 29 percent. No dyskinesias developed in nontreated patients.

In addition to appearing during continued therapy, dyskinesia may develop for the first time after therapy with the associated drug is stopped. Dyskinesia appearing for the first time was observed in 30 percent of 53 patients with chronic schizophrenia in whom long-term neuroleptic therapy was suddenly stopped in a double-blind study.[31] Furthermore, in all of the patients with dyskinesia during therapy there was an intensification when therapy was discontinued.[31] A recent review indicates that in 5 to 40 percent of asymptomatic patients dyskinesias develop upon discontinuation of chronic antipsychotic treatment.[11] In an attempt to reduce the risk of tardive dyskinesia and to increase recognition in latent cases, it has been recommended that in cases of patients with chronic psychoses administration of antipsychotic medication should be periodically stopped (considered a "drug holiday").[12]

Increased incidence of dyskinesias with longer treatment periods has also been documented for L-dopa-induced dyskinesia; these include orofacial as well as cases with limb and truncal involvement. After one month of dopa therapy, the incidence was 17 percent and this increased progressively with each month of treatment up to 73 percent at 12 months.[10] Increased doses appear to increase the incidence of dyskinesia, which occurred in 9 percent of patients receiving 2 grams per day and rose to 44 percent of patients receiving 7½ grams per day.[32]

Orofacial dyskinesias have been reported to occur with the use of virtually all the antipsychotic drugs, including the phenothiazines and butyrophenones. In one series, the maximum incidence was 25 percent of those receiving chlorpromazine, with an incidence of 13 percent of these receiving

TABLE 1.—*Incidence of Dyskinesia According to Sex*

	Males			*Females*		
Source	*Number with Dyskinesia*	*Total Number*	*Percent with Dyskinesia*	*Number with Dyskinesia*	*Total Number*	*Percent with Dyskinesia*
Hunter (1964)[16]	0	200	0	13	250	5
Degwitz (1967)[20]	33	619	5.3	97	672	14
*	14	619	2.3	65	672	9.6
Brandon (1971)[18]	65	426	15	148	484	30
*	17	426	3.9	73	484	15
Kennedy (1971)[13]	17	32	53	22	31	71
*	8	32	25	18	31	58
Fann (1972)[30]	49	144	34	24	57	42
Crane (1973)[11]	27	210	11	23	138	14

*Mild and doubtful cases eliminated.

haloperidol and thioridizine, and 19 percent of those receiving perphenazine and prochlorperazine.[2] Of 63 patients on trifluoperazine for an average of 9.4 years, definite orofacial dyskinesia developed in 41 percent.[13] Treatment in high dosage may increase the incidence of dyskinesia, as suggested by the findings in a study of 175 patients treated with trifluoperazine. At high doses (80 mg per day) for five months, orofacial dyskinesia developed in 26 percent of treated patients, while low dose treatment (16 mg per day) was associated with only a 4 percent incidence.[29] These results take into account an incidence of 17 percent of dyskinesias in placebo treated patients. Similar results, with dyskinesia appearing in 25 percent, were noted when chlorpromazine was administered.[33] Determining the incidence of dyskinesias following use of a specific drug is virtually impossible because most patients have received multiple drugs by the time the abnormal movement is recognized. When it occurs following the changeover from one antipsychotic drug to another, orofacial dyskinesia is more likely related to the discontinued drug than to the new drug which the patient was actually receiving when the dyskinesia was first recognized.

Irreversibility is a widely accepted characteristic of neuroleptic induced dyskinesias. More complete knowledge of the true incidence of remissions after drug termination or upon reduction of dose would be of great value both in understanding the basic pathophysiology as well as in management. Another pertinent question is whether duration of the dyskinesia is a factor in determining reversibility. If this is in fact shown to be the case, then early detection and appropriate management become critical, and suggest the need for periodic termination of neuroleptic treatment.[12] When remissions occur following discontinuation of the drug, they generally occur within a period of weeks to several months. However, six to seven months were required in one case.[17] It has been argued that irreversible oral dyskinesias following administration of phenothiazines were rare when cases with brain damage were excluded and the duration of follow-up exceeded six months.[34] However, brain damage is commonly found in patients with dyskinesia, even in reports which do not consider it as predisposing to dyskinesia.[18,19] There are relatively few studies providing sufficient detailed data to analyze the incidence of remissions, and some of these studies are summarized in Table 2. Of the 354 drug-induced cases followed for more than six months, in 293 or 82 percent dyskinesias continued to occur and in only 17 percent overall were there remissions. High remission rates of 41 percent[17] and 38 percent[35] have been reported, but follow-up duration was mentioned in only one of these series.[17] The apparent irreversibility may reflect the bias of studies made up predominantly of patients who have been in institutions for long periods and have been receiving long-term high dose treatment. Evaluation of an outpatient population who are presumably less incapacitated by psychosis, are younger, have a lower incidence of brain damage and are in a situation in which earlier recognition of dyskinesias might be possible might show different characteristics, especially with regard to incidence and reversibility. It is likely that cases of dyskinesias that have remitted on drug termination have gone unrecognized or unreported. At the present level of knowledge, most cases of orofacial dyskinesias should be considered as irreversible, even when drug use has been terminated.

TABLE 2.—*Remission of Dyskinesia After Drug Termination*

		Dyskinesias Remitted		*Dyskinesias Persistent Follow-up Period*	
Source	*Total Number*	*Number*	*Percent*	*Less Than Six Months*	*More Than Six Months*
Uhrbrand (1960)[17]	17	7	41	2	8
Hunter (1964)[16]	13	0	0	0	13
Degwitz (1969)[31]	273	52/52*	19/19*	0	169†
Edwards (1970)[15]	19	1*	5	0	18‡
Crane (1971)[36]	27	1§	3	0	26§
Hershon (1972)[37]	23	0	0	23	0
Klawans (1974)[23]	7¶	0	0	0	7

*Severity was reduced but dyskinesia was persistent.
†Includes 43 cases in whom severity was increased.
‡Includes five cases which worsened without administration of phenothiazines.
§Net result is shown; actual results include three who improved and two in whom orofacial dyskinesia developed when phenothiazines were not given.
¶Nonpsychotic phenothiazine induced cases.

A possible role of dental malocclusion has been considered in several papers. In one report, the dyskinesia of five patients with nonphenothiazine-related orofacial dyskinesia responded favorably to prosthetic dental therapy to correct the malocclusions.[38] A tendency to relapse when dentures were removed for long periods was commented upon and the authors suggested disruption of dental proprioception as a factor in the genesis of orofacial dyskinesia.[38] The dental status was examined in 368 cases of drug-induced orofacial dyskinesia.[18] Of 207 edentulous patients, dyskinesias developed in 46 percent. By contrast, of 161 patients who either wore dentures or had at least four of their own teeth, dyskinesias developed in only 21 percent. The authors concluded that patients with facial dyskinesias have difficulty in retaining dentures in their mouths, and that the edentulous state was a manifestation of oral dyskinesia rather than a significant cause in this disorder.[18] In several other series, the state of dentition was evaluated and not considered to be a significant factor.[13,15]

Spontaneous orofacial dyskinesias—that is, dyskinesias occurring in the absence of drug exposure and diseases known to be associated with dyskinesias—are considered to be rare, with a reported incidence of 1 to 2 percent.[19,20,39,40] However, several series report that in as many as 10 per cent[2] and 20 percent[18] of patients dyskinesias develop spontaneously. Most spontaneous dyskinesia cases occurred in patients residing in nursing homes or mental hospitals, and most of the patients were of advanced age.[2] As in the drug-induced variety, the spontaneous cases occur more often in women and in those with organic brain disease. Of 285 nonphenothiazine treated mental hospital patients, spontaneous dyskinesia was noted in 29 percent of the women and in 12 percent of the men.[18] Even when the cases of six women with a history of electroconvulsive therapy are eliminated, the incidence remains high at 24 percent. Clinical dementia was observed in half of the 20 men and in three quarters of the 36 women in this series; this was significantly higher than in drug-induced dyskinesia in women.[18] In another series, in more than a third of 40 patients with spontaneous dyskinesias there were diagnoses indicative of organic brain disease.[2] The most common underlying diagnosis, as in drug-induced dyskinesia, was either schizophrenia or affective psychosis.[2] Spontaneous orofacial dyskinesia presents a clinical picture indistinguishable from the drug-induced form.[31] The natural history, including spontaneous remissions, is largely unknown and no extensive series has been reported concerning this aspect. Two cases described in detail were refractory to multiple drug trials,[39] while a favorable response was obtained in most of 15 patients treated with tetrabenazine, pimozide or both.[41]

Basic Mechanisms

A biochemical explanation for orofacial dyskinesias has been advanced, based on several lines of evidence. The first is that neuroleptic drugs appear to act in part by blockade of central dopamine receptors.[42] This blockade has been postulated to then result in a state of "chemical denervation" of dopamine receptors in the striatum.[43] Some of these altered receptors are regarded as then developing "denervation hypersensitivity." Those neurons whose dopamine receptors have become hypersensitive may then respond abnormally to any dopamine to which they are exposed. However, direct proof of this hypothesis is still lacking. Besides receptor blockade, neuroleptics increase synthesis and block the reuptake of dopamine, thereby presenting sensitized receptors with additional amounts of dopamine. These effects would be expected to aggravate a state of receptor hypersensitivity.

A pharmacologic model of two types of dopamine receptors has been formulated.[43] One type of receptor is inhibited by dopamine and is associated with larger striatal neurons. This type is responsible for the rigidity of Huntington's chorea or drug-induced parkinsonism. The other type of receptor is facilitated by dopamine and is associated with smaller striatal neurons. This type is responsible for the chorea of Huntington's chorea and for orofacial dyskinesia. Furthermore, this latter type is blocked by doses of haloperidol and phenothiazines that do not affect the dopamine inhibited receptors. This model would be consistent with the observation that neuroleptic-induced dyskinesias may appear for the first time after reduction of the drug dose, and this is explained as reduced blockade of dopamine facilitated receptors.[43]

Recently, it has become possible to characterize dopamine receptors using dopamine and haloperidol labeled radioactively with tritium.[44] Findings in these studies indicate the presence of two types of dopamine receptors: one which is an agonist and binds dopamine and the other which is an antagonist and exhibits greater affinity for haloperidol. Affinity for the antagonistic binding site was shown by phenothiazines in a rank order similar to their antipsychotic potency. In these studies, fluphenazine and haloperidol had 8 times the potency of chlorpromazine, 52 times the potency of promazine and 200 times the potency of promethazine. Application of these techniques to laboratory models of dyskinesia and to human cases may in the future permit more precise characterization of dopamine receptors and either support or invalidate the dopamine receptor hypothesis.

Certain other phenothiazine drugs are more potent dopamine receptor antagonists than others and this property has been linked to similarity of the molecular conformation to that of dopamine.[45] According to this hypothesis, substitutions on the basic phenothiazine nucleus will determine dopamine receptor blockade activity. Figure 1 indicates that basic phenothiazine nucleus with possible points of substitution indicated as R1 and R2. Halogen substitution at R1 such as in chlorpromazine, fluphenazine or trifluoperazine and substitution at R2 with a piperazine side chain such as fluphenazine or trifluoperazine is associated with high degrees of dopamine receptor blockade and with antipsychotic potency.[45]

Dopaminergic activity altered by neuroleptics may result in dyskinesia upon exposure to another drug. A guinea pig model for dyskinesia showed that stereotyped oral behavior analogous to human orofacial dyskinesia results when chlorpromazine pretreatment for several weeks is followed by omission of drug for one week and then by administration of amphetamine in low doses.[46] In mice, the period of dopaminergic supersensitivity in this paradigm appeared to be brief (observed at two but not nine days) and striatal adenyl cyclase activity was not altered.[47] In monkeys regularly treated with methadone (which is known to block dopamine receptors) and then maintained drug-free for at least two months, conspicuous oral dyskinesias developed in response to low doses of methamphetamine.[48] The authors suggested that the oral dyskinesias resulted from amphetamine-induced stimulation of striatal dopamine receptors made supersensitive by long-term methadone administration. Furthermore, they suggest that human patients maintained on methadone might exhibit hypersensitivity to amphetamine.

Another fundamental aspect of orofacial dyskinesia is that cholinergic and dopaminergic activity are in a state of balance. Certain observed effects suggest that cholingeric hypofunction, besides dopamine receptor hypersensitivity, is partly responsible for dyskinesias. Anticholinergic agents, given to reduce parkinsonism, have been reported to increase the incidence of drug-induced dyskinesias[3,43] and may increase the severity and lower the threshold for appearance.[43] Administration of scopolamine, an anticholinergic agent, worsened voluntary tongue activity, limb chorea and drawing ability in patients with tardive dyskinesias.[49] The opposite effects were observed after the administration of physostigmine, a centrally active cholinergic agent.[49] Similar effects of physostigmine and scopolamine were reported on the orofacial movements of patients with tardive dyskinesia.[50] Reversible orofacial dyskinesias appeared for the first time in six patients treated with anticholinergic agents.[51] Because of these deleterious effects on orofacial dyskinesias, it has been recommended that anticholinergic therapy be avoided as a routine addition to the use of neuroleptics.[43]

Reports of a relationship between extrapyramidal side effects and binding to the cholinergic muscarinic receptor in the brain is additional evidence of cholinergic involvement in orofacial dyskinesia.[52,53] According to this hypothesis, a high incidence of extrapyramidal side effects, including dyskinesia, result from low affinity of a neuroleptic drug for muscarinic receptor binding sites. Conversely, a low incidence of extrapyramidal side effects results from high affinity of a drug for muscarinic binding sites. Furthermore, this model provides a system whereby drugs may be screened for extrapyramidal side effects.[52] Therefore, it is theoretically possible to develop the "ideal" neuroleptic drug which combines potent antischizophrenic activity based on high dopamine receptor blockade and minimal extrapyramidal side effects related to high affinity for muscarinic receptors.

Clinical Therapy

Attempts to treat tardive dyskinesia have been disappointing and largely unsuccessful. At times, initial optimism following a preliminary report of success with a particular drug has been replaced by skepticism when subsequent reports indicate therapeutic failure. In this section, the various pharmacotherapeutic approaches to the treatment of tardive dyskinesias will be reviewed, primarily as to the effects on dopamine at central nervous system synapses.

Dopamine-depleting drugs

Reduction of dopamine should be beneficial, if receptor hypersensitivity to dopamine is a valid model. Reserpine, which depletes catecholamines from intraneuronal storage sites, has been evaluated in several series. Of 16 patients who received 1 mg per day of reserpine along with a neuroleptic, three had improved after one month and two more improved after more prolonged therapy.[54] Of another 16 patients treated with reserpine alone after the neuroleptic was discontinued, seven had improved after one month.[54] Neither withdrawal of the antipsychotic medication nor reserpine-induced rigidity was considered responsible for the improvement. Higher doses of reserpine (from 3 to 5 mg per day) were successful in five patients when lower doses were not effective.[55,56] Once the dyskinesia was controlled, the doses of reserpine were gradually reduced without recurrence of the dyskinesia.[56]

Tetrabenazine, like reserpine, prevents catecholamine storage, but is more rapid in onset and offset and has less hypotensive effect. Beneficial effects on the orofacial dyskinesia of three schizophrenic patients was observed within several days with administration of 75 mg per day of tetrabenazine, but 150 to 300 mg per day were required in a demented patient.[57] Rapid benefit within 24 hours was reported in a dyskinetic patient who received 200 mg of tetrabenazine.[58] In another patient, in whom there were acute dystonia, limb dyskinesia and akathisia after a single injection of fluphenazine, there was prompt response to administration of 150 mg of tetrabenazine.[58] Of six patients treated with 50 to 100 mg of tetrabenazine daily for one week, dyskinesia was abolished temporarily in three patients, but recurred shortly after administration of tetrabenazine was stopped.[59] At dosages up to 150 mg per day of tetrabenazine for six weeks, in 58 percent of 24 dyskinetic patients there was an improvement of 50 percent or more; the abnormal movements were totally suppressed in eight of these patients.[60] However, dyskinesia returned following the discontinuation of treatment with tetrabenazine.[60] Similar results were obtained when the treatment period was extended to 18 weeks, with alleviation of dyskinesia in two of six patients.[61] No further suppression of dyskinesia was achieved despite the longer treatment period or higher doses of up to 200 mg per day.[61]

Remarkable benefit has been reported with the use of tetrabenazine or pimozide (a dopamine receptor blocking agent), or both, in the treatment of 15 patients with spontaneous orofacial dyskinesia.[41] At a dose of 40 to 150 mg per day of tetrabenazine (median dose 75 mg) for 3 to 36 months, dyskinesia disappeared in four and improved in five other patients treated with this drug alone. When 2 to 3 mg per day of pimozide was combined with tetrabenazine, dyskinesia disappeared in all eight patients treated with the combination. Of particular interest is the rarity of recurrence when both drugs were administered together.

Lithium carbonate is widely used for the treatment of acute mania, and is regarded to act by reduction of dopamine at central synapses. One explanation for this effect was enhancement of monoamine oxidation, as suggested by reduced o-methylated and increased deaminated metabolites.[62] In a single patient in one early report[63] and in all six patients in another report, there was benefit from therapeutic doses of lithium.[64] Further studies appear warranted by these favorable reports.

Alpha methyl dopa has been reported to benefit some patients with tardive dyskinesia. There was improvement in two of three patients after treatment with 750 mg per day for one month.[54] By contrast, administration of 500 to 1,000 mg per day for six weeks failed to achieve benefit in any of nine patients with tardive dyskinesia.[65] This drug has two principal effects, namely inhibition of the enzyme dopa decarboxylase resulting in decreased dopamine formation and as a false neurotransmitter that has less "dopaminergic effect" than endogenous dopamine.[66] This dual action suggests this to be a potentially useful agent, but present data are not encouraging.

Alpha-methyl para tyrosine reduces dopamine concentrations by inhibition of the catecholamine synthesizing enzyme tyrosine hydroxylase. Treatment of eight dyskinetic patients with 3 grams per day for three days notably benefited six patients, with less definite reduction in one additional patient.[50]

Dopamine-augmenting drugs

Monoamine oxidase inhibitors increase the amount of dopamine available to synapses and if anything would be expected to worsen dyskinesia. Surprisingly, isocarboxazide, a monoamine oxidase inhibitor, when combined with chlorpromazine was effective in seven of eight patients with oral dyskinesia treated with this combination.[67]

Amantadine has clinical efficacy in the treatment of parkinsonism, and has some dopaminergic action, although preclinical studies have failed to clarify its specific effects.[68] Treatment of tardive dyskinesia with amantadine has been unrewarding as indicated by reports of failure in a combined total of 44 patients.[69-72] Earlier reports of benefit have been criticized as incorrect diagnosis[73] or retracted by the authors after conducting more extensive double blind studies.[74]

Dopamine-blocking drugs

It would appear logical to use drugs that block dopamine receptors to treat a condition that is modeled on hypersensitivity of these receptors. Available and potent receptor blockers include the phenothiazines and butyrophenones, which are also the major dyskinesia-producing agents. As a consequence, a paradoxical situation is encountered in which an antipsychotic drug might be used to control manifestations caused by that same or related drug. It has been observed clinically that increasing the dosage of the same neuroleptic drug the patient already had been receiving may improve orofacial dyskinesia.[75,76] Caution has been suggested in this approach, since a vicious cycle may be initiated of increasingly higher doses being required for dyskinesia suppression.[76]

Of the phenothiazines, thiopropazate in particular has been reported to benefit dyskinetic patients.[77-82] Pronounced reduction or complete disappearance of dyskinesia was reported in four

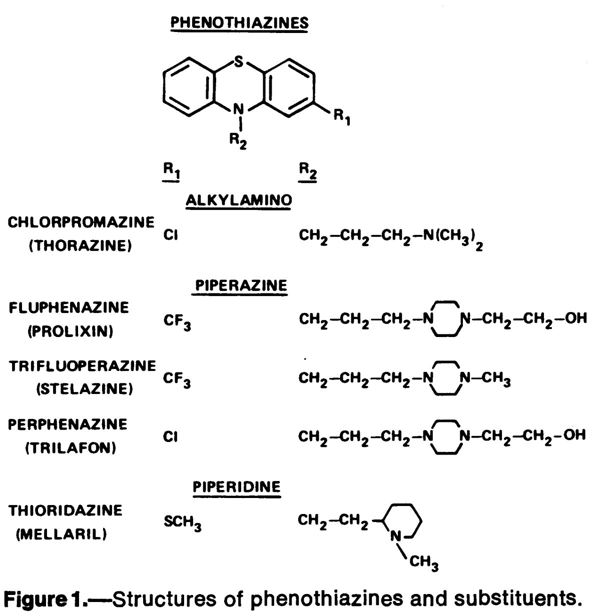

Figure 1.—Structures of phenothiazines and substituents.

of nine patients treated with 40 to 80 mg per day for four weeks.[81] It has been suggested that perphenazine is the active compound resulting from metabolism of thiopropazate, and perphenazine in a daily dose of 24 mg was effective in 14 dyskinetic patients.[81] Both perphenazine and thiopropazate contain the piperazine side chain (see Figure 1) and have potent dopamine and cholinergic receptor blocking action.[44,45,52,53] It has been suggested that the most potent dyskinesia-producing phenothiazines are also the most efficacious in suppressing dyskinesias.[82] Recent studies support a biochemical basis for this correlation.[44,45,52,53]

Haloperidol, a butyrophenone agent, is one of the most potent dopamine receptor antagonists[44] and is similar to the phenothiazines in that it has both dyskinesia producing[83] and dyskinesia alleviating action.[82] In six of 16 patients, orofacial dyskinesias were completely relieved by 8 to 16 mg per day of haloperidol given for four weeks.[82] In most of the patients in whom there was response to therapy with haloperidol, there had been favorable response to tetrabenazine administration in an earlier trial.[82] However, when haloperidol was given for 18 weeks, the initial alleviation of dyskinesias in five of seven patients was progressively lost, despite a doubling of dose.[61] Consequently, the clinical benefit from haloperidol may be of limited duration. As with phenothiazines, a cycle of increasing dosage may be necessary.

Pimozide, a diphenylbutylpiperidine, has relatively specific blocking activity against dopamine receptors.[84] In a double-blind study of 20 dyskinetic patients, pimozide produced significant benefit during a six-week trial.[84] The major side effect was the development of parkinsonism, which is consonant with the view that dyskinesia and parkinsonism represent opposite ends of a spectrum of excessive or insufficient dopaminergic activity.[84] In four patients with nondrug (spontaneous) oral dyskinesia, therapy with 2 to 3 mg per day of pimozide eliminated the dyskinesia.[41] When pimozide and tetrabenazine were combined, dyskinesia was totally suppressed in all eight patients receiving the combination. Furthermore, recurrence was rare when the two drugs were used in combination.

Cholinergic drugs

A balance of cholinergic and dopaminergic function is considered necessary for normal motor activity.[49] Cholinergic hypofunction has been considered dyskinesia-inducing and administration of anticholinergic drugs may actually increase the incidence of orofacial dyskinesia.[3,43] It has been recommended that therapy with antiparkinsonian agents with anticholinergic action, such as trihexyphenidyl and benztropine, be avoided as a routine addition to treatment with antipsychotic drugs.[43]

Use of cholinomimetic agents, by contrast, may have beneficial effect in dyskinesias. Physostigmine is an anticholinesterase that crosses the blood brain barrier and increases the concentration of brain acetylcholine.[85] Intravenous injection of 1 mg of physostigmine lessened tongue movements in ten of 12 dyskinetic patients, and improved drawing ability in four of six patients tested.[49] However, these favorable results have not been found by others. After 1 mg of intravenously given physostigmine, only a slight reduction of dyskinesia was noted in four patients and no benefit in four others.[50] In another report of seven patients, no benefit or an increase in the dyskinesia was observed after the intravenous injection of 1 mg of physostigmine.[86]

Deanol, which is the dimethylaminoethanol salt of para acetamidobenzoic acid, is regarded as a choline precursor, and augments the cholinergic system.[87] Two brief reports indicated clear benefit in two patients receiving 600 mg per day[88] and in another receiving 1,600 mg per day.[89] However, subsequent reports indicate therapeutic failure despite doses of 1,600 mg per day in two patients[90] and in another series, despite treatment with 1,200 to 1,600 mg per day in 11 patients.[91] These results indicate a need for continued clinical trials to determine the role of deanol in the management of tardive dyskinesia.

In a patient with dyskinesia refractory to deanol (maximum of 2 grams per day for three weeks), there was response to 16 grams per day of choline chloride, after lower doses had been ineffective during the first week of treatment.[92] When administration of choline was stopped, dyskinesia returned.

Additional therapeutic agents

Pyridoxine (vitamin B_6) neutralizes the effects of L-dopa administration in patients with parkinsonism[93] including the side effect of dopa-induced dystonia.[94] Based on these observations, ten patients with neuroleptic-induced dyskinesia were treated with 300 mg of pyridoxine per day for 10 to 14 days, but with no benefit.[95]

Therapy with papaverine, a smooth-muscle relaxant used clinically as a cerebral vasodilator, improved orofacial dyskinesias in three patients when they were given 300 to 600 mg per day.[96]

Imbalance between serotonin and dopamine in the basal ganglia has been considered as contributing to orofacial dyskinesias.[97] In an attempt to increase brain serotonin, 6 grams per day of the serotonin precursor L-tryptophan was administered to four dyskinetic patients in a double-blind study.[97] This treatment temporarily suppressed dyskinesia in all the patients, but a tendency to relapse in a few days was observed.[97] This unsustained benefit was ascribed to temporary compensation of catecholamine predominance by enhancement of serotonin. Another serotonin precursor, 5 hydroxytryptophan, failed to benefit the one dyskinetic patient in whom it was tried.[98]

Clonazepam, an anticonvulsant of the benzodiazepine group, was reported to improve the dyskinesia in 42 patients treated with one to three mg per day.[99] This brief report offers the prospect of effective therapy for tardive dyskinesia, if these results are corroborated by other workers.

Therapeutic Approach and Summary

Present data on tardive dyskinesia suggest it is a symptom complex and not a single disease entity. Additional knowledge regarding the significance of such factors as duration of dyskinesia, the effect of continued administration of neuroleptics after recognition of dyskinesia and the optimal dose as well as duration of various therapeutic approaches may indicate these to be salient variables. It may be most appropriate to consider several biochemical mechanisms at the same time, with particular focus on the balance of cholinergic and dopaminergic activity.

When the results summarized in this review are considered, an appropriate approach might be to therapeutically challenge dyskinetic patients with different categories of rapidly acting agents.[50,101] This approach should include cholingeric agents (such as physostigmine), anticholinergic agents (such as benztropine), dopamine-depleting agents (such as tetrabenazine) and dopamine-blocking agents (such as pimozide and haloperidol). The responses to such a series of drugs may then provide a more rational basis to pursue specific therapeutic courses subsequently.

As discussed, administration of antipsychotic medication should periodically be stopped and studies made for the presence of dyskinesia as well as to determine the need for continued treatment.[12,100] When dyskinesia is initially recognized, administration of the antipsychotic drug should be discontinued, or at least reduced to the minimum therapeutic level. Recent preclinical and clinical studies indicate that clozapine, a dibenzodiazepine, has potent antipsychotic activity and the lowest incidence of extrapyramidal side effects.[52,53,102] This drug may be especially suited for the patient in whom neuroleptics are required but in whom orofacial dyskinesia is present. Early recognition and, ultimately, prevention may be the only effective means of reducing the incidence of this disorder.

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